The calm before the storm: Clinical observations of Middle East Respiratory Syndrome (MERS) patients

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Abstract

BACKGROUND:

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection emerged in 2012. The majority of cases occurred in the Kingdom of Saudi Arabia and the disease carries a high case fatality rate.

METHODS:

We present three MERS-CoV cases and highlight the salient clinical features and laboratory, and radiographic characteristics.

RESULTS:

Although all nasopharyngeal samples were negative, MERS CoV infection was confirmed by reverse transcription-polymerase chain reaction of the E gene (UpE) and open reading frame (ORF1b) on sputum samples. The Ct value of the ORF1 gene was 24.8-29.11. One patient had been on immune suppressive agent and two patients had diabetes mellitus. The average length of hospital stay was 10.6 days. Two patients received ribavirin and IFN-a2b in addition to supportive management. The clinical course for these patients started with a febrile period lasting five days, a reduction in fever was coinciding with increased respiratory rate and oxygen requirements. All patients were discharged home. None of the 50 contacts tested positive for MERS-CoV.

CONCLUSION:

Resolution of the fever was accompanied by an increase in oxygen requirements and respiratory rate also lasting several days. This was followed by resolution of all symptoms and return to normal.

Since the emergence of the Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) infection in Saudi Arabia in 2012 [1], the World Health Organization (WHO) reported a total of 2090 cases including 730 deaths [2]. Previous studies described clinical characteristics of MERS-CoV patients and the hospital outcome [3–6]. The utility of nasopharyngeal swabs and lower sputum samples were mentioned but were not clearly described. In this paper, we describe three patients who had negative nasopharyngeal swabs but continued to have symptoms and sputum testing was confirmed the diagnosis of MERS-CoV. MERS-CoV testing was done on either Dacron-flocked nasopharyngeal swabs or sputum samples and were tested with real-time reverse-transcription polymerase chain reaction [7].

The first case is a 56-year-old Saudi gentleman with erosive rheumatoid arthritis and had been on adalimumab and daily Prednisone (5 mg) was admitted with generalized tiredness, weakness, nausea, and dizziness. He had no nausea, vomiting, or diarrhea. The patient also described cough and sputum production. He had no history of contact with animals. He was awake, alert, and oriented to time, place, and person. Maximum temperature was 37.5^0C. Oxygen saturation was 96% on 2 liters, blood pressure was 120/70 mm Hg, and respiratory rate was 18/minute. Lung examination revealed vesicular breathing and end inspiratory crackles. Chest x-ray revealed bilateral peripheral infiltrates and computerized axial tomography showed nonspecific bilateral patchy parenchymal airspace disease. A nasopharyngeal swab was negative for both MERS-CoV and influenza by PCR and laboratory data are shown in table 1. He was treated as a community acquired pneumonia. Sputum test for MERS-CoV was positive. He developed increasing oxygen requirements, and chest x-ray worsened despite broad spectrum antibiotics. He was gradually weaned off supplemental O_2 therapy and was discharged home.

The second case is a 52-year-old Saudi gentleman with history of diabetes mellitus and dyslipidemia was admitted with cough, sputum production and fever. The patient has no nausea, vomiting or diarrhea. The patient had no animal contact and no raw milk ingestion. Vital signs were: temperature 38.5^0C, blood pressure 120/70 mm Hg, and respiratory rate 18/minute. There was no skin rash. Lungs examination revealed decreased air entry at the basis with evidence of consolidation in the left lower zone posteriorly

with egophony. A nasopharyngeal swab was negative for MERS-CoV and influenza by PCR. Chest radiograph showed left lower lobe infiltrate and he was admitted. He was treated as a community acquired pneumonia and then oseltimavir was added. He continued to have fever of 38^0C and developed faint skin rash that was thought maybe secondary to medication versus viral exanthem. A repeat chest x-ray showed progression of consolidation in the right upper lobe. Five days after admission, his oxygen requirement started to increase (figure 1). A sputum sample was positive for MERS-CoV by PCR. He continued to have intermittent fever with increasing oxygen requirement. He was started on interferon-α2b and Ribavirin. A repeat sample for MERS-CoV was negative from the nasopharyngeal however, and a sputum sample was positive for MERS-CoV (Table 1). He required intensive care management and later he was discharged home.

The third case is a 53-year-old Saudi gentleman with history of hepatitis B carrier, diabetes mellitus was admitted with six days history of cough productive of whitish sputum and fever. He had mild nausea and vomiting, and loose bowel movement. He had no contact with animal, no raw milk ingestion, and no history of travel. Vital signs were: temperature of 39^0C, O2 saturation 96% on room air, and respiratory rate was 16/minute. He had a faint erythematous rash in the anterior upper chest area. Lungs had vesicular breathing and end-inspiratory crackles in the right base posteriorly. Nasopharyngeal swab for MERS-CoV was negative and a sputum sample was positive for MERS-CoV (table 1). Chest x-ray showed patchy airspace disease in the right lower lobe and a CT scan revealed extensive patchy infiltrate. He was treated with interferon-α2b and ribavirin. A repeat MERS testing was negative and the patient was discharged home.

The three patients were febrile for about 5 days and then fever subsided (Figure 1). The reduction in fever coincided with increased respiratory rate (figure 1) and increased inspiratory oxygen requirements. A total of 50 contracts tested negative based on nasopharyngeal swabs.

The three cases were confirmed MERS-CoV infection based on PCR testing of lower respiratory samples with Ct value <37 Initial case series indicated the value of nasopharyngeal swab testing for MERS-CoV diagnosis [7]. In two studies of the dynamics of MERS-CoV, lower respiratory samples showed higher Ct values and were detected later in the course of the disease [7,8]. The WHO recommends that both upper and lower respiratory tract specimens be collected whenever possible [9]. Thus, it is important to have repeat testing and lower respiratory samples in patients presenting with pneumonia to confirm or rule out MERS-CoV [8]. A total of 50 contracts tested negative based on nasopharyngeal swabs as recommended [9]. Variable contact results were cited in the different studies of 11–19% based on screening of 28–42 family contacts [10–12]. In a study of 462 family members, the positivity rate was 3% by PCR [13]. Variable transmissions within healthcare settings were also cited. An investigation of >200 healthcare workers showed two laboratory-confirmed cases [14]. In other settings, healthcare outbreaks were initiated by a single patient such as in Al-Hasa, Riyadh, Jeddah and South Korea [15,16]. It was observed that patients were clinically stable with no tachypnea and then they had tachypnea and increased oxygen requirement by day 5-6. Patients with MERS-CoV at the time of admission were less likely to have tachypnea (27%) compared to controls (60%), and less likely to have respiratory distress (15% vs. 51%) [3]. The timeline of the development of respiratory distress is within the reported time from onset to admission to intensive care unit and mechanical ventilation [17]. The exact mechanism for the development of respiratory distress coinciding with resolution of fever is interesting. MERS infection appears to go through different phases. Phase 1 is the phase of virologic replication and is characterized by fever and constitutional symptoms. This is followed by phase 2 (immunopathological phase) characterized by resolution of fever and increased oxygen desaturation coupled with radiological deterioration. Phase 3 is characterized by either further deterioration or resolution of symptoms as the case in these three patients. There are no standard therapy for MERS-CoV and the use of interferon and ribavirin was suggested [18–20], however, there are no randomized controlled trials of anti-viral therapy. Two of the three cases in the present report were treated with interferon-α2b and ribavirin and all patients recovered. The timing of the initiation of anti-viral agents seems to be important determinants of the

response to therapy. The best time to initiate anti-viral agents is the phase of virologic replication before the development of immunopathological phase. The first use of anti-viral in clinical setting was in a case series of five patients [18]. Therapy was initiated at a median time from admission to therapy of 19 (range 10-22) days and none survived [18]. A subsequent study of 20 patients received ribavirin and interferon within a median of 3 days [range 0-8] after diagnosis [21]. The 14 day-survival rate was 70% of 20 patients in the treatment group compared with 29% of the comparator group (p=0·004) with no survival advantage at 28 days [21]. Thus, the use of interferon-α2b and ribavirin combination is a possible therapy and should be used early in the disease to have an impact.

In conclusion, these three patients showed a three-phase illness characterized by initial phase of fever and clinical stability probably representing viral replication. This phase was followed by a second phase of immunologic phase with clinical and radiographic deterioration and subsequent stabilization. Treating physicians should be aware of the clinical course of the disease as well as the yield of respiratory samples in the detection of MERS-CoV.

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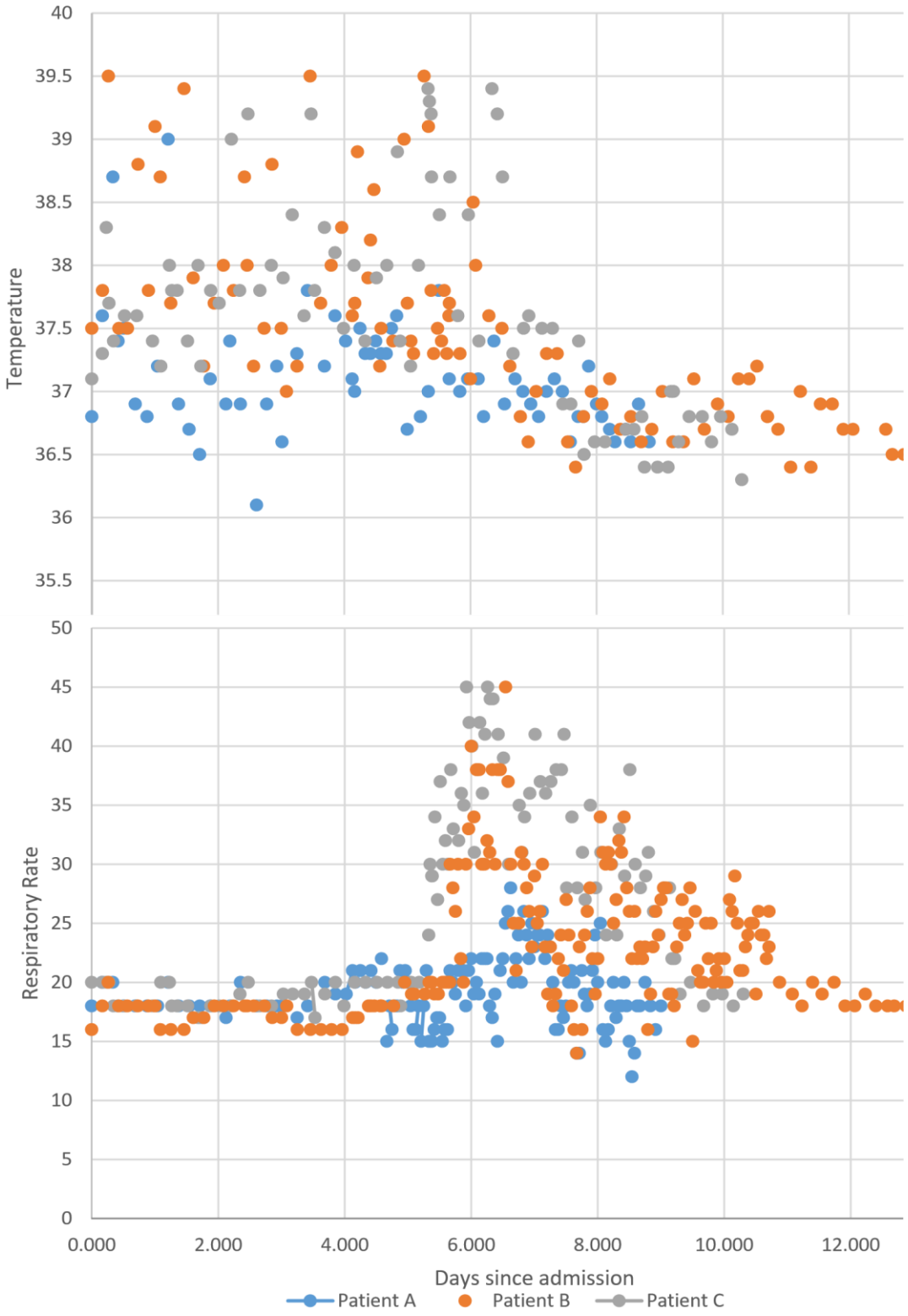
Table 1: A Summary of the clinical, laboratory and radiographic manifestations of the reported MERS-CoV cases:

	Case 1	Case 2	Case 3
Age/Gender	56/M	52/M	53/M
Days from onset to admission	7	4	5

Comorbidities and medications	Rheumatoid arthritis. Prednisone; Adalimumab	Diabetes Mellitus; dyslipidemia	Chronic HBV carrier, Diabetes Mellitus
Animal Contacts	No	No	No
Nasopharyngeal Swap 1	Negative	Negative	Negative
Nasopharyngeal Swap 2	Negative	Negative	
Sputum	Positive	Positive	Positive
UpE gene	30.04	29.03	24.45
Orf	27.9	29.11	24.8
Nasopharyngeal Swap 3	Negative (5 days from first positive)	Not done	Not done
Ribavarin and Interferon	None	Yes	Yes
Fever	Yes	Yes	Yes
Cough	Yes	Yes	Yes
GI symptoms	Nausea	None	Nausea, vomiting, diarrhea

Initial CXR	Bilateral peripheral infiltrate	Consolidation right upper lobe	Patchy air space disease right lower lobe
Initial WBC	5100	1700	1800
Hepatic Panel	Elevated	Normal	Elevated
Length of hospital stay	9	13	10

Figure 1: A Scattered Graph Showing the Timeline Course of Temperature and Respiratory Rate by time from admission. The Figure shows that resolution of fever by Day 6 coincided with increased respiratory rate.


Temperature
40
39.5
39
38.5
38
37.5
37
36.5
36
35.5
Respiratory Rate
50
45
40
35
30
25
20
15
10
5
0
0.000
2.000
4.000
6.000
8.000
10.000
12.000
Days since admission
Patient A
Patient B
Patient C